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MYERS BIGEL SIBLEY & SAJOVEC			EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/783,054

Applicant(s)

CHILKOTI ET AL.

Examiner

CARALYNNE HELM

Art Unit

1615

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 18 January 2011.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 2-9, 11-16, 18-31 and 51-63 is/are pending in the application.
- 4a) Of the above claim(s) 3, 15, 20, 22-27, 52 and 54-59 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 2, 4-9, 11-14, 16, 18, 19, 21, 28-31, 51, 53 and 60-63 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Note to Applicant: References to paragraphs in non-patent literature refer to full paragraphs (e.g. 'page 1 column 1 paragraph 1' refers to the first full paragraph on page 1 in column 1 of the reference)

Election/Restrictions

To summarize the current election, applicants elected the species where the article is an orthopedic implant, the protein-resistant head group is tri(sarcosine), and the surface portion comprises metal.

Claims 3, 15, 20, 22-27, 52, and 54-59 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species, there being no allowable generic or linking claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

The four factual inquiries of *Graham v. John Deere Co.* have been fully considered and analyzed in the rejections that follow.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 2, 4-7, 9, 11-14, 16, 18-19, 21, 28-31, 51, 53, and 60-63 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chapman et al. (previously cited) view of Hawker et al. (previously cited), Zhang et al. (previously cited), Morgan (previously cited), Allbritton et al. (previously cited), and Leckband et al. (previously cited).

Broadly, the invention claimed is a method of using a device (article) with a coating of polymer brushes on its surface that are attached to the device surface via a linking layer. These polymer brush bristles have protein resistant groups (kosmotropes)

that confer protein resistance to the surface of the device. Chapman et al. teach this concept where their coating resists protein and bacterial adhesion (see figure 1 and paragraphs 114-117; instant claim 1). A self assembled monolayer of alkanethiol is formed on an article that is coated with gold (see paragraph 153 and 159; instant claims 2, 4 and 6). The exposed end is converted into a reactive functional group (initiator terminated alkanethiol) such that a polymer can be grafted (see paragraph 153; instant claim 7). This polymer contains several head groups (branches) that resist the adsorption of proteins and bacteria (see paragraph 153 and 162). Chapman et al. teach such coatings for articles that are in-dwelling, such as artificial bone or joint replacements (orthopedic implant) (see paragraph 64; instant claim 21). Chapman et al. also teach self assembled monolayers that display different protein and bacteria resistant head groups. Tri(sarcosine) is in the set demonstrated to be particularly effective (see figures 4-5 and paragraph 144; instant claims 12-14). Chapman et al. go on to teach that in addition to protein and bacteria resistance, their polymer layers can be further modified by covalently attaching ligands that bind specific biomolecules (see paragraph 124; instant claim 18-19). Protein molecules as well as peptides are particularly envisioned as these ligands (see paragraph 121; instant claim 18). Since a receptor is a chemical structure that provides a site of attachment, these envisioned proteins qualify as receptors (see instant claim 19). Upon exposure to fluid with biomolecules, adsorption of general biomolecules (e.g. protein) and bacteria is resisted such that binding of those biomolecules for which the ligand is specific occurs (see paragraph 124; instant claim 32). The *in vivo* contacting of the device of Chapman et al.

with biological fluids is clearly envisioned in their contemplation of in-dwelling medical devices as substrates for their taught coating (see paragraph 42). Chapman et al. do not explicitly teach the claimed polymer brushes with tri(sarcosine) head groups.

In view of the teachings of Chapman et al., it would have been obvious to one of ordinary skill in the art at the time of the invention to select tri(sarcosine) as the protein and bacteria resistant head group to include in the surface bound polymer of their invention, where an orthopedic implant is the coated article and an alkanethiol layer linking the polymer to the article substrate. Since the use of a device for its intended purpose is obvious, the contacting of such a device to a biological fluid such that selective binding can occur to the attached ligands while repelling non-specific adhesion would also have been obvious based upon the teachings of Chapman et al. This reference does not explicitly teach that the orthopedic implant is a dental prosthesis, that the polymer is formed of monomers with a vinyl core monomer group and a protein resistant head group coupled thereto, produced via surface initiated polymerization, or that the linking layer is patterned on the substrate.

Morgan teaches a dental implant with a threaded region that is composed of biocompatible material (e.g., titanium) and anchored into cortical bone (orthopedic implant) (see column 2 lines 28-35; instant claims 21 and 53). The implant is taught to be temporary, remaining implanted for four to six weeks (*in vivo* contacting with blood) (see column 1 lines 55-67; instant claims 28-31 and 51). The lower end of this range meets the limitation of up to approximately 26 days and month as recited in claims 60-63.

Zhang et al. teach a polymer utilized to resist protein adhesion on implant surfaces (see page 691 column 1 paragraph 10). Specifically these polymers are composed of monomers of methacryloyloxyethyl phosphorylcholine, an acrylate monomer with a coupled phosphorylcholine group, and butyl methacrylate (see page 691 column 2 paragraph 1 and page 700 column 1 paragraph 2; instant claim 11). Chapman et al. teach phosphorylcholine as an envisioned protein resistant head group whose performance in this capacity was not as good as tri(sarcosine) (see Chapman et al. figure 5).

Hawker et al. teach polymer brush patterns built from a self assembled monolayer on a substrate (see abstract; instant claims 38). In particular, a substrate surface that can be composed of a variety of envisioned materials (e.g. gold or tungsten) serves as the base for the polymer (see column 8 lines 9-18). Subsequently a compound (linking layer) containing a group reactive with the substrate surface on one end and providing an initiator on the other end is applied to the surface (see column 8 lines 56-67 and column 9 lines 27-29). The material is then contacted with a polymerizable composition composed of monomers that sequentially form polymers at these initiation sites (see column 9 lines 60-64). One preferred technique utilizes an initiator that generates a free radical polymerization and vinyl monomers (see column 10 lines 10-17; instant claims 9, 28, and 51). The resulting polymers are taught to be between 28 and 38 nm in length (see figure 3; instant claims 16 and 48). This technique is taught in particular in the production of patterned surfaces, where the initiator containing molecules are placed in particular locales on the substrate (see column 8

lines 53-64; instant claims 5 and 37). In one example, Hawker exemplifies the compound that makes up the linking layer as an initiator terminated alkanethiol that forms a patterned or continuous self assembled monolayer (column 13 lines 46-50 and 58-63; instant claims 4-7 and 36-39).

Allbritton et al. teach surface grafted polymers to modify the surface of medical devices and confer desired properties (see paragraph 12). Particular monomers that resist protein adhesion are chosen for surface initiated polymerization (see paragraph 42). Allbritton et al. go on to teach various grafting densities for these monomers that include polyethylene glycol monomethoxyl acrylate (see paragraphs 34 and 42). Specifically, grafting densities from approximately $5 \mu\text{g}/\text{cm}^2$ ($50 \text{ mg}/\text{m}^2$) to $60 \mu\text{g}/\text{cm}^2$ ($600 \text{ mg}/\text{m}^2$) are taught (see figure 4A and paragraph 24; instant claim 17).

Leckband et al. teach polymer brushes on a substrate as a protein resistant surface (see abstract). In particular, Leckband et al. discuss that the graft density (polymer surface density) is a key parameter in controlling the degree of protein adsorption retardation (see page 1143 paragraph 4). Leckband et al. also teach that this density is optimized based upon the target environment (e.g. size, geometry and concentration of proteins) (see page 1143 paragraph 4).

Since Chapman et al. and Zhang et al. teach particular chemical moieties on medical device surfaces to resist adsorption of undesired biological species upon implantation, it would have been obvious to one of ordinary skill in the art to combine their teachings. In addition, it also would have been obvious to combine the teachings of Chapman et al. and Hawker et al. because both teach surface bound polymeric

coatings attached via self assembled monolayers of reactive alkanethiol groups on metallic surfaces. Further, it also would have been obvious to this ordinarily skilled artisan to select the dental implant of Morgan as an orthopedic implant suitable for the invention of Chapman et al. Based upon these teachings it would have been obvious to one of ordinary skill in the art at the time of the invention to prepare and implant the dental implant of Morgan with the polymer layer having functional groups as taught by Chapman et al. via the method of Hawker et al. using an acrylate monomer coupled with tri(sarcosine) instead of the phosphorylcholine as taught by Zhang et al. (see instant claims 44-46). A free radical polymerization initiated from a self assembled monolayer of initiator-terminated alkanethiols on a gold surface would follow from this combination of references yielding the claimed stem and plurality of branches (see instant claim 28). Further modification of the resulting layer of polymer brush molecules by covalently attaching a protein (ligand), based upon the teachings of Chapman et al., would also have been obvious (see instant claims 18 and 50). The implantation of the device, as taught by Morgan, would result in its contacting blood for greater than one day and up to 26 days as well as one month.

In view of the teachings of Allbritton et al. of polymers with functional groups that were taught by Chapman et al. to function similarly to tri(sarcosine), it would have been well within the purview of one of ordinary skill in the art to optimize the grafting density of the polymers of Chapman et al. in view of Zhang et al., Hawker et al., and Morgan in order to achieve the desired degree of protein adsorption resistance. The lower end of the grafting density range for the protein resistant polymers falls within the range

instantly claimed (see instant claims 28 and 51). Therefore claims 2, 4-7, 9, 11-14, 16, 18-19, 21, 28-31, 51, 53, and 60-63 are obvious over Chapman et al. in view of Zhang et al., Hawker et al., Morgan, Allbritton et al. and Leckband et al.

Claims 8 and 28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chapman et al. in view of Zhang et al., Hawker et al., Morgan, Allbritton et al. and Leckband et al. as applied to claims 2, 4-7, 9, 11-14, 16, 18-19, 21, 28-31, 51, 53, and 60-63 above, and further in view of Guan et al.

Chapman et al. in view of Zhang et al., Hawker et al., Morgan, Allbritton et al. and Leckband et al. make obvious the method of instant claim 28. This modified reference does not explicitly teach that the polymerization is carried out via atom transfer radical polymerization.

Guan et al. teach that although it was known to polymerize vinyl monomers via free radical polymerization, atom transfer radical polymerization was also a viable means of polymerizing these same monomers (see column 1 lines 58-59 and column 2 lines 10-19). Thus as a known option within their technical grasp, it would have been obvious to one of ordinary skill in the art at the time of the invention to employ atom transfer radical polymerization as the polymerization method instead of free radical polymerization in the invention of Chapman et al. in view of Zhang et al., Hawker et al., Morgan, Allbritton et al. and Leckband et al. where vinyl monomers are used as the core group. Therefore claims 8 and 28 are obvious over Chapman et al. in view of Zhang et al., Hawker et al., Morgan, Allbritton et al., Leckband et al., and Guan et al.

Response to Arguments

Applicants' arguments, filed January 18, 2011, have been fully considered. Due to the amendment to the claims, the rejections of claim 8 under 35 USC 103(a) no longer meet the claim limitations and are hereby withdrawn. A new grounds of rejection is provided that meets the limitations of claim 8.

Regarding the rejection under 35 USC 112, first paragraph:

While applicants argue that the self-assembled monolayer generated by Flynn et al. is not polymeric as is instantly claimed, this difference is not sufficient by itself to overcome the rejection. Luk et al. (Langmuir 2000 16:9604-9608) teach a self assembled monolayer of compounds utilizing an alkanethiol terminated compound that assembles on a gold surface as is the embodiment of focus in the rejection. These layers are examined for their ability to resist protein adhesion as assessed by their resistance to cell grown in an *in vitro* cell culture assay (see figure 3). Compounds 1a and 1b have the same protein resistant terminal group but differ in that 1b has a longer poly(methylene) chain than 1a (see figure 1). When patterned onto a culture surface such that a small discrete area is uncovered, 1a has a better ability to maintain the cell growth in the uncovered areas over 25 days than 1b. Since these compounds only differ in the length of their respective poly(methylene) chain lengths, this data points to the improved stability of monolayers of protein resistant gold-alkanethiol bound compounds with longer chain length. In the instant case, the length of the protein resistant polymer

would be longer than that of Flynn et al. whose stability degraded over 35 days in a physiological environment. Moreover, the instant polymer compounds would also have protein resistant moieties along the full length of the polymer as opposed to just the end as is the case for both Luk et al. and Flynn et al. This further points to the increased ability of the instant gold-alkanethiol linked layers to stably resist protein adsorption for durations beyond those taught by Flynn et al. Although the gold-alkanethiol linked layer is susceptible to some degree of degradation over time in physiological media, this break down by itself is not necessarily sufficient to eliminate its protein resistance. For these reasons, the scope of enablement rejection made under 35 USC 112, first paragraph is hereby withdrawn.

Regarding the rejection under 35 USC 103(a) over Mittelman in view of Bialk et al., Zhang et al., Ejaz et al., Chapman et al., Allbritton et al., and Leckband et al.:

Applicants' argument that Bialk et al. does not teach a polymer of the same form as that claimed, namely a polymer brush generated by surface initiated polymerization is persuasive because their polymer's point of connection to the surface could be mid-chain which is not the same as that generated by surface initiated polymerization. Therefore this rejection is hereby withdrawn.

Regarding the rejection under 35 USC 103(a) over Chapman et al. in view of Hawker et al., Zhang et al., Morgan, Allbritton et al., and Leckband et al.:

Applicants argue that none of the references separately or in combination teach the claimed invention and that Zhang et al. do not teach polymer brushes. While Zhang et al. do not teach a brush configuration for their polymer, the teachings of Chapman et al. already teach polymer brushes that resist protein absorption onto the surface of medical devices. Zhang et al. teach particular polymers that are known to also resist protein absorption and this functionality would have been expected to be retained upon orientation as brushes since the protein resistant functional groups would still be displayed on the surface. Chapman et al. together with Hawker et al., Zhang et al., and Morgan make obvious the method of providing a metal orthopedic implant with a layer of polymer brushes composed of methacrylate monomers with tri(sarcosine) head groups (vinyl monomer core having a protein-resistant head group) that are polymerized by surface initiated polymerization base upon an alkanethiol initiator (linking layer). These references are silent concerning the discrete surface density of the protein resistant polymers and Allbritton et al. along with Leckband et al. fill this void.

Applicants argue that the grafted polymers of Allbritton et al. are not the same type of polymer as the brush polymers instantly claimed. Allbritton et al. teach photo-initiated graft polymerization of polymers onto a surface (see paragraph 12). Ikada et al. teach that graft polymerization onto a surface creates initiating functional groups on the surface (see Biomaterials 1995 15:725-736, especially page 726 column 1 paragraph 1). The result in both graft polymerization and the surface initiated polymerization of the instant invention is a surface initiated polymerization of polymer yielding one end of a series of polymer chains bound to the surface and the other end free. Both also teach

the polymerization of vinyl monomers to their respective surfaces as well as the inclusion of monomers with functional groups to resist protein absorption (see Allbritton et al. paragraphs 14 and 42). Therefore both methods yield polymer brushes built from the polymerization of monomers with protein resistant functional groups. For this reason the artisan of ordinary skill in the art would have been motivated to combine these teachings with those of Chapman et al., Hawker et al., Zhang et al., and Morgan to help guide the selection of a polymer grafting density in order to achieve a protein resistant surface. Leckband et al. further encourage this artisan to optimize the grafting density to achieve the desired degree of protein resistance. The nature of the substrate (e.g. metal vs. polymer) does not alter the final polymer product once the polymerization has been initiated, therefore this difference does not diminish the relevance of the teachings of Allbritton et al. to those of the other cited references. The linking layer of the instant claims merely serves as a surface localized source of initiation for the polymerization. The graft polymerization process of Allbritton et al. also has a surface initiated polymerization, so the absence of a linking layer in their teachings is not so significant that they are no longer relevant to those to the other cited references or the instant invention. Allbritton et al. teaches a range for the polymer grafting density that overlaps with that instantly claimed and the teachings of Leckband et al. encourage optimization of this level to achieve the desired protein resistance, therefore the addition of these teachings to those of Chapman et al. together with Hawker et al., Zhang et al., and Morgan renders the instant invention obvious.

In response to applicants' argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971). In addition, the combination of known elements that are instantly claimed is an obvious modification of what was already known in the art and applicants have not demonstrated the criticality of the claimed grafting density range, linking layer initiator, or any other claimed element to distinguish the instant invention over the prior art.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CARALYNNE HELM whose telephone number is (571)270-3506. The examiner can normally be reached on Monday through Friday 9-5 (EDT).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Robert A. Wax can be reached on 571-272-0623. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.